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EASL Clinical Practice Guidelines: Management of cholestatic liver diseases

European Association for the Study of the Liver*

Keywords: **Primary biliary cirrhosis; Primary sclerosing cholangitis; Overlap syndrome; Immunoglobulin G4-associated cholangitis; Drug-induced cholestatic liver disease; Genetic cholestatic liver disease; Cholestatic liver diseases in pregnancy; Intrahepatic cholestasis of pregnancy; Fatigue; Pruritus**

1. Introduction

EASL Clinical Practice Guidelines (CPG) on the management of cholestatic liver diseases define the use of diagnostic, therapeutic and preventive modalities, including non-invasive and invasive procedures, in the management of patients with cholestatic liver diseases. They are intended to assist physicians and other health-care providers as well as patients and interested individuals in the clinical decision-making process by describing a range of generally accepted approaches for the diagnosis, treatment and prevention of specific cholestatic liver diseases. The clinical care for patients with cholestatic liver diseases has advanced considerably during recent decades thanks to growing insight into pathophysiological mechanisms and remarkable methodological and technical developments in diagnostic procedures as well as therapeutic and preventive approaches. Still, various aspects in the care of patients with cholestatic disorders remain incompletely resolved. The EASL CPG on the management of cholestatic liver diseases aim to provide current recommendations on the following issues:

- Diagnostic approach to the cholestatic patient.
- Diagnosis and treatment of primary biliary cirrhosis (PBC).
- Diagnosis and treatment of PBC–autoimmune hepatitis (AIH) overlap syndrome.
- Diagnosis and treatment of primary sclerosing cholangitis (PSC).
- Diagnosis and treatment of PSC–AIH overlap syndrome.
- Diagnosis and treatment of immunoglobulin G4-associated cholangitis (IAC).

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Abbreviations: AIH, autoimmune hepatitis; AIP, autoimmune pancreatitis; AMA, antimitochondrial antibodies; AP, alkaline phosphatase in serum; ASMA, anti-smooth muscle antibodies; BRIC, benign recurrent intrahepatic cholestasis; CCA, cholangiocarcinoma; CF, cystic fibrosis; CFALD, cystic fibrosis-associated liver disease; CPG, Clinical Practice Guidelines; CT, computed tomography; DILI, drug-induced liver injury; EASL, European Association for the Study of the Liver; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; FDG-PET, (^{18}F)-fluoro-deoxy-D-glucose positron emission tomography; FXR, farnesoid X receptor; γGT, γ-glutamyltranspeptidase in serum; HCC, hepatocellular carcinoma; IAC, immunoglobulin G4-associated cholangitis; IAIHG, International Autoimmune Hepatitis Group; IBD, inflammatory bowel disease; IgG, immunoglobulin G in serum; IgG4, immunoglobulin G4 in serum; MRCP, magnetic resonance cholangiopancreatography; NASH, non-alcoholic steatohepatitis; PBC, primary biliary cirrhosis; PDC-E2, E2 subunit of the pyruvate dehydrogenase complex; PSC, primary sclerosing cholangitis; PIIINP, procollagen-3-aminoterminal propeptide; UC, ulcerative colitis; ULN, upper limit of normal; US, ultrasound.

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- Diagnosis and treatment of drug-induced cholestatic liver diseases.
- Diagnosis and treatment of genetic cholestatic liver diseases.
- Diagnosis and treatment of cholestatic liver diseases in pregnancy.
- Treatment of extrahepatic manifestations of cholestatic liver diseases.

Table 1a
Categories of evidence.

Grade	Evidence
I	Randomized controlled trials
II-1	Controlled trials without randomization
II-2	Cohort or case-control analytic studies
II-3	Multiple time series, dramatic uncontrolled experiments
III	Opinions of respected authorities, descriptive epidemiology

A panel of experts selected by the EASL Governing Board in May 2008 wrote and discussed these guidelines between June and November 2008. These guidelines have been produced using evidence from PubMed and Cochrane database searches before 1 October, 2008. Where possible, the level of evidence and recommendation are cited (Tables 1a, 1b). The evidence and recommendations in these guidelines have been graded according to the Grading of Recommendations Assessment Development and Evaluation (GRADE system) [1]. The strength of recommendations thus reflects the quality of underlying evidence which has been classified in one of three levels: high [A], moderate [B] or low-quality evidence [C]. The GRADE system offers two grades of recommendation: strong [1] or weak [2] (Table 1b). The CPG thus consider the quality of evidence: the higher, the more likely a strong recommendation is warranted; the greater the variability in values and preferences, or the greater the uncertainty, the more likely a weaker recommendation is warranted. Where no clear evidence exists, guidance is based on the consensus advice of expert opinion in the literature and the writing committee.

2. Diagnostic approach to cholestasis

Cholestasis is an impairment of bile formation and/or bile flow which may clinically present with fatigue, pruritus and, in its most overt form, jaundice. Early biochemical markers in often asymptomatic patients include increases in serum alkaline phosphatase (AP) and γ-glutamyltranspeptidase (γGT) followed by conjugated hyperbilirubinemia at more advanced stages. Cholestasis may be classified as intrahepatic or extrahepatic. Intrahepatic cholestasis may result from hepatocellular functional defects or from obstructive lesions of the intrahepatic biliary tract distal from bile canaliculi. Cholestasis may also be related to mixed mechanisms in diseases such as lymphoma [2]. By convention, cholestasis is considered chronic if it lasts >6 months. Most chronic cholestatic diseases are purely intrahepatic, whereas sclerosing cholangitis may affect small and large intrahepatic and/or extrahepatic bile ducts. Asymptomatic patients are generally identified when routine laboratory tests are being performed or during work-up for another disease when an increase is noted in the serum level of AP and/or γGT. Isolated serum γGT elevation has little specificity for cholestasis, and may also result from enzyme induction in response to alcohol or drug intake. Isolated serum AP elevation is seen in cholestatic liver diseases including certain rare disorders (e.g., progressive familial intrahepatic cholestasis (PFIC) 1 & 2, bile acid synthesis defects), but may also result from rapid bone growth (e.g., in children), bone disease (e.g., Paget's disease), or pregnancy. The cut-off levels of serum AP and γGT requiring diagnostic work-up are debated: AP levels higher than 1.5 times the upper limit of normal (ULN) and γGT levels >3× ULN have been proposed. The differential diagnosis of cholestatic disor-

Table 1b
Evidence grading (adapted from the GRADE system [1]).

Evidence	Notes	
High quality	Further research is very unlikely to change our confidence in the estimate of effect	A
Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate	B
Low quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Any change of estimate is uncertain	C
Recommendation		
Strong	Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost	1
Weak	Variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, higher cost or resource consumption	2